Catalytic Enantioselective Chlorination and Bromination of *β*-Keto Esters

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Dedicated to Professor *Albert Eschenmoser* on the occasion of his 75th birthday

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The Ti(TADDOLato) complexes dichloro[(4*R*,5*R*)-2,2-dimethyl-*α*,*α*,*α*′,*α*′-tetraphenyl-1,3-dioxolane-4,5-dimethanolato(2 –)-*O*,*O*′]titanium ((*R*)-**1a**) and dichloro[(4*R*,5*R*)-2,2-dimethyl-*α*,*α*,*α*′,*α*′-tetra(naphthalen-1-yl)-1,3-dioxolane-4,5-dimethanolato(2 –)-*O*,*O*′]titanium ((*R*)-**1b**) are efficient catalysts for the electrophilic enantioselective chlorination and bromination of *β*-keto esters with *N*-chlorosuccinimide (NCS) and *N*-bromosuccinimide (NBS), respectively. With 5 mol-% of catalyst at room temperature an enantioselectivity of up to 88% ee could be obtained for the chlorination reaction. Under comparable conditions, bromination reactions are slower and less stereoselective.

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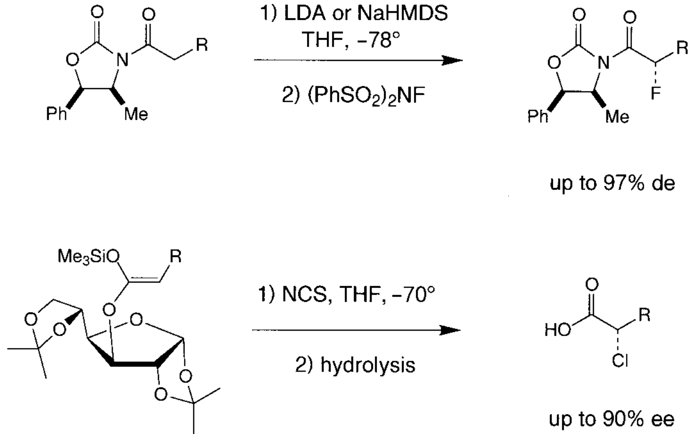
1. Introduction. – Carbon–halogen bond-forming reactions concomitant with the selective generation of a new stereogenic center are rare processes. They are essentially restricted to fluorination reactions (for reviews, see [1]), although scattered reports concerning other halogens have also appeared (see, *e.g.*, [2]). Fluoroorganic drugs are very important in medicinal chemistry, *e.g.*, by virtue of their improved resistance against oxidative degradation in biological systems as compared to their nonfluorinated counterparts. Stereoselective fluorination has been achieved in recent years by the use of two related approaches, exclusively. Chiral, enantiomerically pure N–F reagents (for reviews, see [3]) that behave as electrophiles are able to formally transfer F^+ to a preformed enolate, thereby affording an *α*-fluoro-carbonyl derivative in varying degrees of enantioselection [4]. On the other hand, the use of oxazolidinone chiral auxiliaries allows the diastereoselective fluorination of aliphatic acids, analogously *via* enolate formation and with achiral N–F reagents [5]. For a diastereoselective electrophilic chlorination, a very similar approach has been reported by *Duhamel* who used diacetone glucose as the chiral auxiliary, as part of silyl-ketene acetals [6]. By a similar concept, a diastereoselective bromination of allyl glycosides has been achieved with tribromides [7]. Examples of non-catalytic stereoselective halogenation reactions based on the chiral auxiliary principle are illustrated in *Scheme 1*.

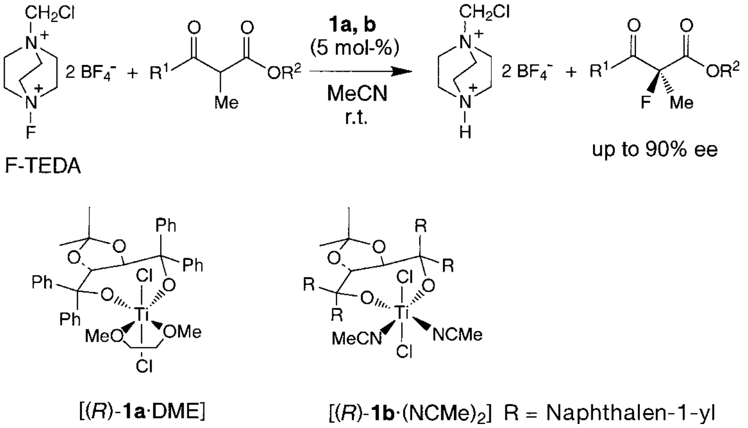
As part of a research program aimed at the development of catalytic methods for the generation of new C–X (X = halogen) stereogenic centers, we recently reported the first catalytic and enantioselective electrophilic fluorination of *β*-keto esters [8]. It was shown that fluorine can be introduced into such substrates with F-TEDA (= 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis[tetrafluoroborate], also called *Selectfluor*™; TEDA = triethylenediamine) [9] and in the presence of 5 mol-% of isolated, analytically pure [$TiCl_2$(TADDOLato)] complexes [10][1]) of the type **1**[2]) as

Scheme 1



catalysts, whereby enantioselectivities up to 90% ee were obtained (*Scheme 2*). Prior to this work, we also demonstrated *1*) the enantiospecific C–H activation and iodination of cycloocta-1,5-diene coordinated to an Ir^I complex containing a chiral ferrocenyl diphosphine [11], and *2*) the Ru^{II}-mediated halogen-exchange reaction with well-defined cationic 16-electron fluoro complexes [12].

Scheme 2



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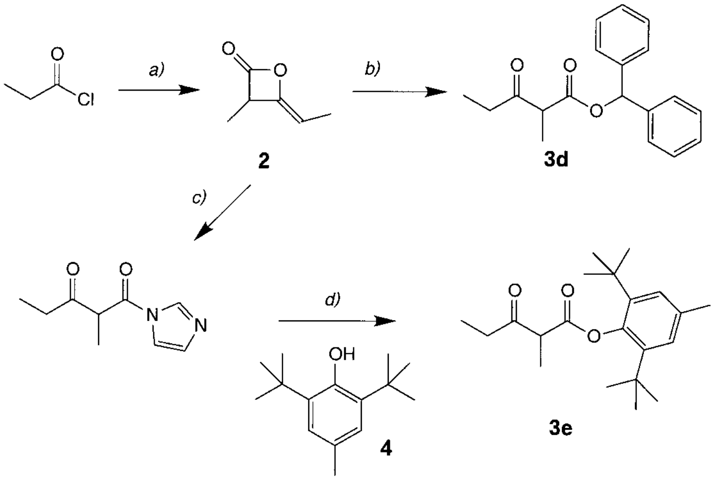
1) For a comprehensive review on TADDOLs and their use in asymmetric synthesis, see [10]. We thank Prof. *Dieter Seebach* for a copy of the manuscript prior to publication.

2) (*R*)-**1a**: Dichloro[(4*R*,5*R*)-2,2-dimethyl-*α*,*α*,*α*′,*α*′-tetraphenyl-1,3-dioxolane-4,5-dimethanolato(2 –)-*O*,*O*′]-titanium. (*R*)-**1b**: Dichloro[(4*R*,5*R*)-2,2-dimethyl-*α*,*α*,*α*′,*α*′-tetra(naphthalen-1-yl)-1,3-dioxolane-4,5-dimethanolato(2 –)-*O*,*O*′]titanium. The two corresponding TADDOL ligands are commercially available.

2. Results and Discussion. – 2.1. *Preparation of β-Keto Esters.* α-Monosubstituted β-keto esters are the best-suited substrates for studies concerning enantioselective electrophilic substitutions in the α position due to the impossibility of racemization of the products obtained. Moreover, by virtue of the two different C=O functionalities, these materials are useful building blocks for further transformations, after the generation of a new quaternary stereogenic center based on carbon–halogen bond formation. Substrates **3** (*cf. Scheme 4* and *Table 1*) with variable substituents at the keto group were obtained by classical routes [13], namely *Claisen* condensation (**3a**), aldol addition followed by oxidation (**3b**), or transesterification (**3c**). Furthermore, by reacting the methylketene dimer **2** [14] with a variety of alcohols, it should be possible to obtain a range of 2-methyl-3-oxopentanoates with ester groups of variable steric demand [14][15]. However, whereas **2** did indeed react with Ph_2CHOH to afford derivative **3d** *via* nucleophilic catalysis (*Scheme 3*), it proved problematic to obtain the corresponding ester with the bulky 'butylated hydroxytoluene' (BHT; **4**). Several experiments with acidic and basic catalysts have shown that esterification was, in all cases, slower than the concomitant decomposition of **2**, and that only trace amounts of the desired ester **3e** could be detected. This problem was finally overcome by first converting **2** to a more stable *N*-acylimidazole derivative [16], which reacted with **4**, after activation with CF_3COOH, to yield the strongly enolized **3e** (55% enol content in $CDCl_3$) in remarkably high yield (*Scheme 3*). All new β-keto esters **3a**–**e** were isolated in analytically pure form as oily materials (which partly solidified upon standing) after column chromatography, and were fully characterized.

Scheme 3



a) Et_3N, *t*-BuOMe; 56%. *b*) Ph_2CHOH, 4-pyrrolidinopyridine, CH_2Cl_2; 78%. *c*) Imidazole, CH_2Cl_2. *d*) CF_3COOH, **4**; 96%.

2.2. *Enantioselective Chlorination and Bromination.* In the course of our catalytic fluorination experiments of β-keto esters with F-TEDA [8], we observed, in particular in the case of slow-reacting substrates, the formation of the corresponding α-Cl derivatives in low amounts. The Cl-atom incorporated into the by-product should originate from the catalyst, since, in similar experiments with catalysts not containing chlorine, such as $[Cp_2Ti(OTf)_2]$, no chlorination reaction was ever observed. How the Cl ligands are transformed into an electrophilic chlorination agent under the applied reaction conditions is at present unclear. However, one can tentatively assume that the reagent analogous to F-TEDA (Cl-TEDA) is formed by a halide-exchange process, indicating also that chloride dissociation from complexes **1** is an easily occurring process. A typical HPLC chromatogram of a reaction mixture, which shows the presence of the fluorinated main product, accompanied by the Cl compound and some unreacted starting material, is shown in the *Figure*.

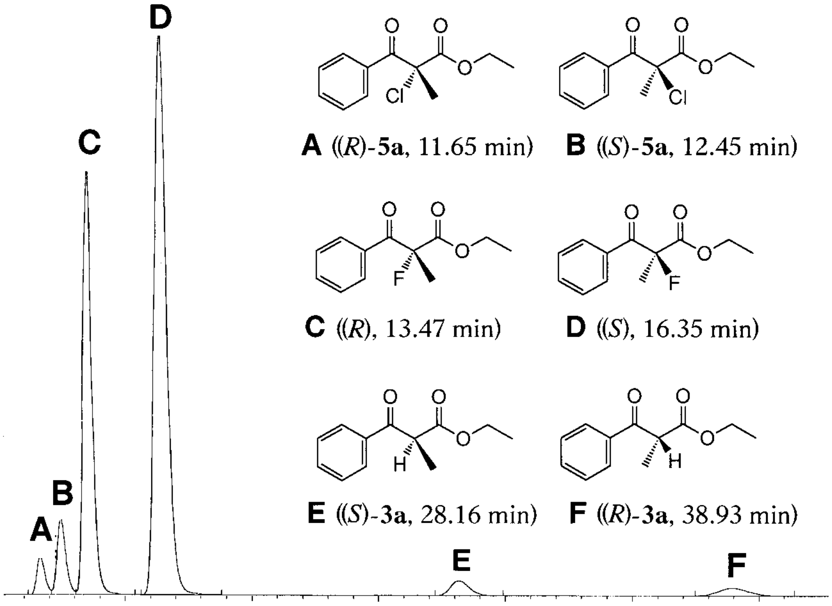
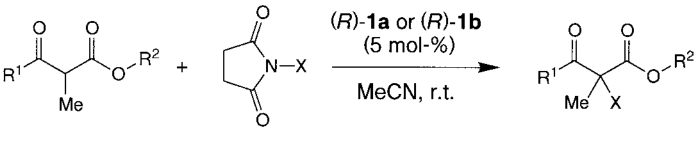


Figure. *HPLC Trace of a fluorination reaction mixture showing the presence of the chlorination product and some unreacted starting material (*for the enantiomers of these two compounds the absolute configurations indicated are arbitrary*). Conditions: DAICEL Chiralcel OB-H* column; 96:4 (*v/v*) hexane/i-PrOH eluent; 0.5 ml/min flow; detection at 254 nm.

The observations described above prompted us to undertake a first study on the catalytic enantioselective chlorination and bromination of β-keto esters, very much in analogy to the corresponding fluorination reaction. For this purpose, we chose *N*-chlorosuccinimide (NCS) and *N*-bromosuccinimide (NBS) as the prototype electrophilic chlorination and bromination agents, respectively (*Scheme 4*).

Scheme 4



3a - e (racemic)

NCS X = Cl
NBS X = Br

5a - e X = Cl
6a, d X = Br

We were pleased to find that the new catalytic halogenation of β-keto esters **3** proceeded smoothly at room temperature in the presence of 5 mol-% of the catalysts (*R*)-**1a** or (*R*)-**1b**, to afford the products **5** as oily materials in good to almost quantitative isolated yields (*Table 1*; see also *Table 2* for details concerning the determination of enantioselectivity by HPLC).

Table 1. *Results for the Catalytic Enantioselective Chlorination and Bromination*

Substrate/ Product	Substituents	Selectivity[a] (reaction time)[b]		$[\alpha]_D$ of **5**[c]	Yield[d] [%]
		Catalyst (*R*)-**1a**	Catalyst (*R*)-**1b**		
		Chlorination			
3a/**5a**	$R^1 = Ph$, $R^2 = Et$	40% ee (< 10 h)	59% ee (1 h)	+ 61.0 (*c* = 1.025, 59.0% ee)	85%
3b/**5b**	R^1 = Naphthalen-2-yl, $R^2 = Et$	48% ee (< 10 h)	63% ee (2 h)	+ 62.3 (*c* = 0.77, 63.1% ee)	87%
3c/**5c**	$R^1 = Me$, $R^2 = Bn$	60% ee (40 min)	60% ee (< 30 min)	– 4.0 (*c* = 1.215, 48.0% ee)	85%
3d/**5d**	$R^1 = Et$, $R^2 = Ph_2CH$	83% ee (1 h)	88% ee (< 1 h)	– 5.6 (*c* = 1.17, 88.2% ee)	94%
3e/**5e**	$R^1 = Et$, $R^2 = 2,6\text{-}(t\text{-Bu})_2\text{-}4\text{-Me}-C_6H_2$	13% ee (< 15 h)	11% ee (< 15 h)	– 1.2 (*c* = 0.985, 11.4% ee)	97%
		Bromination			
3a/**6a**	$R^1 = Ph$, $R^2 = Et$	8% ee (40 min)	3% ee (4 h)[e]	+ 8.8 (*c* = 0.96, 8.5% ee)	84%
3d/**6d**	$R^1 = Et$, $R^2 = Ph_2CH$	23% ee (< 30 min)	6% ee (1 h)[e]	– 5.1 (*c* = 1.08, 22.8% ee)	90%

[a] Reactions were performed at room temperature with 5 mol-% catalyst; for details, see *Exper. Part*. ee Values were determined by HPLC; see *Table 2*. [b] Approximate time to complete conversion as detected by TLC. [c] Measured in MeOH solution at room temperature on a sample of indicated ee. [d] Isolated yields for single experiments; for exact conditions, see *Exper. Part.* [c] Incomplete conversion due to catalyst decomposition.

Table 2. *HPLC Conditions for Analytical Enantiomer Separation*

Compound	HPLC Column[a]	Eluent composition hexane/i-PrOH (*v*/*v*)	Flow [ml/min]	UV Detection wavelength [nm]	Retention times[b] [min]
5a	*OJ*	90 : 10	1	254	6.2, *8.3*
5b	*OJ*	90 : 10	1	254	8.9, *11.3*
5c	*OJ*	99 : 1	0.7	210	23.9, *26.9*
5d	*OJ*	90 : 10	1	210	*8.0*, 10.3
5e	*OD-H*	99.6 : 0.4	0.7	210	22.8, *29.9*
6a	*OJ*	90 : 10	1	254	6.8, *9.9*
6d	*OJ*	90 : 10	1	210	*8.1*, 9.7

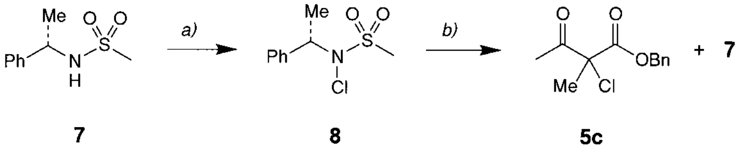
[a] *Daicel Chiralcel*, 250 × 4.6 mm

[b] Retention times for *major enantiomers* are indicated in *italics*.

Inspection of the data provided by *Table 1* indicates that the enantioselectivity and rate of the chlorination reaction depends on a subtle interplay between steric properties of catalyst and substrate. Thus, the bulkier catalyst (*R*)-**1b** leads to faster reactions and tends to give higher ee values than its counterpart (*R*)-**1a**, with the highest ee of 88% so far obtained in the chlorination of the diphenylmethyl ester **3d**. Furthermore, it appears that, in the series **3a**–**d**, sterically demanding substituents on either the keto group (**3a**, **3b**) or the ester group (**3c**, **3d**) increase the ee values of the products **5a**–**d**. However, the case of keto ester **3e** does not fit into this simple scheme. We speculate that the steric bulk in this substrate might prevent an effective coordination to the metal center, thus slowing the metal-catalyzed chlorination to such an extent that the uncatalyzed background chlorination of the enol form effectively competes with the catalytic pathway. This explanation is in line with the long reaction time and the high enol content of **3e**.

To compare the catalytic chlorination reaction with the stochiometric reaction with chiral chlorinating agents, we prepared *N*-chlorosulfonamide **8** from sulfonamide **7** by *N*-chlorination with bleach [17] (*Scheme 5*). The uncatalyzed reaction of **8** with keto ester **3c** proceeded slowly (20% conversion in 6 h) to yield **5c** with essentially no enantioselectivity (1% ee). When the reaction was catalyzed by the addition of 5 mol-% of the achiral catalyst $CpTiCl_3$ (Cp = η^5-cyclopentadienyl), quantitative formation of, again, almost racemic **5c** (0.3% ee) took place within 20 min. However, 5 mol-% of catalyst (*R*)-**1a** led to quantitative conversion within 30 min and afforded an ee value of 52.6%. These results show that a simple chiral chlorinating agent is not able to significantly induce stereoselectivity in chlorination reactions. This is probably due to too few and sterically poorly defined interactions of reagent and substrate in the transition state. On the other hand, when the substrate undergoes complex formation with the catalyst, a better differentiation between the enantiotopic faces of the enolized substrate becomes possible. This will lead to higher stereoselectivities, even when the chlorinating agent is attacking the substrate without any prior direct interaction with the metal center (external attack).

Scheme 5



a) NaOCl (aq.), NBu_4HSO_4, CH_2Cl_2; 95%. *b*) **3c**, MeCN, 5 mol-% $CpTiCl_3$ or (*R*)-**1a**.

When NBS (*N*-bromosuccinimide) was used as an electrophile in the analogous catalytic bromination reaction (*Scheme 4* and *Table 1*), the products were obtained also in excellent yields under very mild conditions (note that these results are in contrast to a recent literature report on the preparation of **6a** from **3a**, where rather harsh conditions – NBS, dibenzoyl peroxide, CCl_4, reflux 10 h – were applied [18]). However, the most striking feature observed for the bromination reaction is the dramatic drop in enantioselectivity as compared to the corresponding catalytic chlorination of the same substrates. Whereas keto ester **3a**, for example, could be chlorinated with an enantioselectivity of 59% ee, the corresponding bromination afforded almost racemic product only (3% ee). This observation cannot be explained by an uncatalyzed background reaction, as only small amounts of bromination products are formed after several hours at room temperature in the absence of a catalyst.

In the HPLC chromatograms of the raw bromination products, minor amounts of the corresponding chlorinated products were detected, again showing that Cl ligands from the catalysts **1** are available to undergo halogen-exchange reactions under the reaction conditions applied.

3. Conclusion. – We have shown that the well-known *Lewis* acidic [$TiCl_2$(TADDOLato)] complexes are suitable catalysts for the electrophilic halogenation of β-keto esters. This new catalytic reaction offers a mild method for the generation of a new stereogenic center by carbon–halogen bond formation. Enantioselectivities up to 88% ee could be obtained for chlorinations with NCS and commercially available TADDOL ligands. Although the mechanistic details of this reaction are still to be worked out, we assume that the role of the catalyst consists in triggering the enolization of the β-keto ester substrate *via* complexation to the Ti-atom in a chelating fashion. This activation process is followed by an external stereoselective attack by the electrophilic halogenating agent. Similar mechanistic considerations have been reported by *Evans* and *Nelson* for an enantioselective amination of enolizable substrates catalyzed by Mg *Lewis* acids [19].

Current work in our laboratory, besides addressing mechanistic questions, aims at extending the applicability of catalytic halogenation to enolizable substrates other than β-keto esters, as well as at improving the properties of the catalyst.

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Experimental Part

General. Ethyl 2-methyl-3-oxo-3-phenylpropanoate (**3a**) was prepared from propiophenone, diethyl carbonate, and NaH according to a general procedure [20]. *Benzyl 2-methyl-3-oxobutanoate* (**3c**) was prepared from $PhCH_2OH$ and ethyl 2-methylacetoacetate by a literature procedure [21]. The synthesis and characterization of complexes [(*R*)-**1a** · (DME)] · MeCN and [(*R*)-**1b** · (MeCN)] is reported in [8]. NCS and NBS (*Fluka*) were used as received. Reagent-grade MeCN was stored over 3-Å molecular sieves. Syntheses were performed under an inert atmosphere. Catalytic runs were performed under air in closed vessels. TLC: *Merck* silica-gel *60 F_{254}* plates. Flash chromatography (FC): silica gel *60*, *Fluka*. Optical-rotation measurements were performed at r.t. NMR: 300 MHz (^{1}H) and 75.5 MHz (^{13}C), in $CDCl_3$; chemical shifts δ in ppm and coupling constants J in Hz; Me_4Si ($\delta(^1H) = 0$) and $CDCl_3$ ($\delta(^{13}C) = 77$) were used as internal standards. The number of attached protons was determined by DEPT-135. For enolized compounds, selected signals for the enol form are given.

4-[(Z)-Ethylidene]-3-methyloxetan-2-one (**2**) [14][22]. Synthesis adapted from *Sauer* [14]. In a three-necked 2000-ml flask equipped with a mechanical stirring unit were placed 160 ml of Et_3N (1.15 mol, distilled over Na) and 1000 ml of *t*-BuOMe (distilled over NaH). To the stirred soln. were added 100 ml of propionyl chloride (1.15 mol, freshly distilled), first in portions of 10 ml (exothermic reaction) and then at a rate to keep the reaction temp. below the boiling point of the solvent (55°), but without external cooling. The resulting thick suspension was stirred 1 d at r.t., then quenched with 300 ml of ice-H_2O, stirred until all precipitates had dissolved, and the pale-yellow organic phase was efficiently washed with four 100-ml portions of ice-H_2O. After drying ($MgSO_4$) and removal of the solvent, the remaining yellow liquid was purified by distillation (54°/20 mbar to 50°/15 mbar) to yield 36.3 g (56%) of **2** as pale-yellow liquid having on irritant smell. Purity by ^{1}H-NMR: 97%, the only detectable impurity being propionic anhydride. The compound was degassed and stored under Ar at $-20°$; at r.t. it polymerized within a few weeks. ^{1}H-NMR: 1.41 (d, $J = 7.6$, Me–C(3)); 1.68

(*dd*, $J = 7.0$, 1.4, *Me*–CH=C(4)); 3.99 (*qd*, $J = 7.6$, 1.4, H–C(3)); 4.76 (*qd*, $J = 7.0$, 1.4, H–C=C(4)). ^{13}C-NMR: 9.3 (Me); 12.0 (Me); 48.3 (CH); 95.1 (CH); 147.2 (C); 169.9 (C).

Ethyl 2-Methyl-3-(naphthalen-2-yl)-3-oxopropanoate (**3b**). To an LDA soln. (from 3.0 ml of $(i\text{-Pr})_2NH$, 30 ml of THF, and 21 mmol of BuLi at – 20°) was added dropwise 2.4 ml of ethyl propionate (21 mmol) at – 78° and, after stirring for 30 min, a soln. of 3.124 g of naphthalene-2-carbaldehyde (20 mmol) in 10 ml of THF within 30 min. The mixture was stirred 2 h (– 78° to r.t.) and quenched with 20 ml of sat. aq. NH_4Cl soln. and 50 ml of *t*-BuOMe. The org. phase was washed with 0.1M aq. HCl and H_2O, dried ($MgSO_4$), and evaporated. To the crude product dissolved in 50 ml of CH_2Cl_2 were added 5 g of powdered molecular sieves (4 Å), 0.5 g of $NaHCO_3$, and, under stirring at 0°, a total of 6.0 g of finely powdered pyridinium chlorochromate (27.8 mmol) in portions. After stirring overnight at r.t., filtering through Al_2O_3, and washing the filter with *t*-BuOMe, the greenish filtrate was evaporated and the raw product submitted to FC (*t*-BuOME/hexane 1:10) to yield 2.569 g (50%) of **3b**. Faintly yellow oil. R_f (*t*-BuOMe/hexane 1:5) 0.31. IR (film, NaCl): 3059*w*, 2983*m*, 2939*w*, 1738*s*, 1682*s*, 1627*m*, 1596*w*, 1467*m*, 1453*m*, 1374*m*, 1353*m*, 1279*m*, 1216*m*, 1196*s*, 1125*m*, 1084*m*, 1033*m*, 981*w*, 937*m*, 862*m*, 819*w*, 758*w*. ^{1}H-NMR: 1.16 (*t*, $J = 7.2$, *Me*CH_2O); 1.56 (*d*, $J = 7.1$, *Me*CH); 4.13, 4.17 (*C* and *D* of A_3CD, $J_{AC} = J_{AD} = 7.1$, $J_{CD} = 10.8$, $MeCH_2O$); 4.54 (*q*, $J = 7.1$, MeC*H*); 7.48–7.64 (*m*, 2 arom. H); 7.83–8.06 (*m*, 4 arom. H); 8.51 (*s*, 1 arom. H); enol form (2.5%): 1.36 (*t*, $J = 7.3$, *Me*CH_2O); 1.91 (*s*, *Me*–C=C); 4.31 (*q*, $J = 7.1$, $MeCH_2O$); 13.10 (*s*, OH). ^{13}C-NMR: 13.8 (Me); 13.9 (Me); 48.3 (CH); 61.3 (CH_2); 124.0 (CH); 126.8 (CH); 127.7 (CH); 128.5 (CH); 128.6 (CH); 129.6 (CH); 130.3 (CH); 132.4 (C); 133.1 (C); 135.6 (C); 170.9 (C); 195.7 (C). MS (EI): 256 (10, M^+), 210 (3.5), 155 (100), 127 (37). Anal. calc. for $C_{16}H_{16}O_3$ (256.30): C 74.98, H 6.29; found: C 75.16, H 6.37.

Diphenylmethyl 2-Methyl-3-oxopentanoate (**3d**). To **2** (1.30 g, 11.6 mmol) in 4 ml of CH_2Cl_2 was added 1.84 g of diphenylmethanol (10 mmol) and 50 mg of 4-pyrrolidinopyridine (0.34 mmol) at 0°. After 5 min, the ice bath was removed, and the mixture was stirred 1 d at r.t. Purification by FC (*t*-BuOMe/hexane 1:10) gave 2.316 g (78%) of **3d**. Colorless solid. M.p. 33.3–33.9°. R_f (*t*-BuOMe/hexane 1:5) 0.49. IR (KBr): 3028*w*, 2973*w*, 2940*w*, 1737*s*, 1705*s*, 1494*w*, 1448*m*, 1361*w*, 1344*w*, 1193*m*, 1098*m*, 962*m*, 762*m*, 744*m*, 700*m*. ^{1}H-NMR, keto form: 0.99 (*t*, $J = 7.2$, *Me*CH_2); 1.37 (*d*, $J = 7.1$, *Me*CH); 2.39 (*dq*, $J = 18.2$, 7.2, 1 $MeCH_2$); 2.51 (*dq*, $J = 18.2$, 7.2, 1 $MeCH_2$); 3.62 (*q*, $J = 7.2$, MeC*H*); 6.90 (*s*, Ph_2CHO); 7.24–7.39 (*m*, 10 arom. H); enol form (7.5%): 1.13 (*t*, $J = 7.5$, *Me*CH_2); 1.90 (*s*, *Me*C=COH); 2.33 (*q*, $J = 7.6$, $MeCH_2$); 6.94 (*s*, Ph_2CHO); 12.60 (*s*, OH). ^{13}C-NMR: 7.5 (Me); 12.7 (Me); 34.6 (CH_2); 52.8 (CH); 77.7 (CH); 126.9 (CH); 127.0 (CH); 128.0 (CH); 128.1 (CH); 128.5 (CH); 128.5 (CH); 139.6 (C); 139.6 (C); 169.5 (C); 205.9 (C); enol form: 126.9 (CH); 127.8 (CH); 128.5 (CH); 140.4 (C). HR-MS (MALDI): 319.131 ($[M + Na]^+$; calc. 319.131). Anal. calc. for $C_{19}H_{20}O_3$ (296.37): C 77.00, H 6.80; found: C 76.90, H 6.67.

*2,6-Di-(*tert*-butyl)-4-methylphenyl 2-Methyl-3-oxopentanoate* (**3e**). To 2.204 g of *2,6-di-(*tert*-butyl)-4-methylphenol* (**4**; BHT; 10.0 mmol) and imidazole (8.17 mg, 12.0 mmol) in 10 ml of CH_2Cl_2, **2** (1.346 g, 12.0 mmol) was added dropwise at 0° with stirring. After 20 min at r.t. the resulting soln. was cooled to – 10° (ice/EtOH), and CF_3COOH (0.92 ml, 12.0 mmol) was added dropwise to give a suspension, which was stirred for 20 min at – 10°, then for 10 h at r.t. and for 12 h at 40°. The mixture was diluted with 100 ml of *t*-BuOMe and washed with brine (3 × 100 ml). The org. phase was dried ($MgSO_4$) and evaporated. Purification by FC (*t*-BuOMe/hexane 1:20) yielded 3.207 g (96%) of **3e** as colorless oil that solidified on standing. M.p. 58–74°. R_f (*t*-BuOMe/hexane 1:10) 0.53. IR (KBr): 2999*m*, 2969*s*, 2873*m*, 1740*m*, 1721*s*, 1653*m*, 1646*m*, 1616*m*, 1419*m*, 1363*m*, 1261*s*, 1228*s*, 1199*s*, 1180*s*, 1143*m*, 1113*s*, 1105*s*, 1059*m*, 862*m*, 845*m*. ^{1}H-NMR: keto form (45%): 1.11 (*t*, $J = 7.2$, *Me*CH_2CO); 1.28 (*s*, *t*Bu); 1.32 (*s*, *t*-Bu); 1.52 (*d*, $J = 7.2$, *Me*CH); 2.31 (*s*, Me–C(4')); 2.64 (*dq*, $J = 18.6$, 7.3, 1 $MeCH_2CO$); 2.94 (*dq*, $J = 18.6$, 7.3, 1 $MeCH_2CO$); 3.88 (*q*, $J = 7.2$, H–C(2)); 7.11 (*q*, $J = 0.6$, 2 arom. H); enol form (55%): 1.29 (*t*, $J = 7.5$, *Me*CH_2CO); 1.32 (*s*, 2 *t*-Bu); 2.03 (*s*, Me–C(2)); 2.32 (*s*, Me–C(4')); 2.43 (*q*, $J = 7.5$, $MeCH_2CO$); 7.13 (*q*, $J = 0.6$, 2 arom. H); 12.84 (*t*, $J = 0.9$, OH). ^{13}C-NMR: mixture of keto and enol forms: 7.5; 10.6; 11.0; 13.0; 21.4; 21.5; 25.9; 31.3; 31.4; 35.1; 35.1; 35.2; 36.4; 53.2; 94.2; 126.9; 127.0; 134.4; 134.7; 141.8; 141.9; 142.1; 145.2; 146.0; 170.0; 174.5; 178.3; 206.0. EI-MS: 333 (1, $[M + H]^+$), 332 (0.6, M^+), 220 (100), 205 (99). Anal. calc. for $C_{21}H_{32}O_3$ (332.48): C 75.86, H 9.70; found: C 75.62, H 9.77.

General Procedure for Catalytic Halogenations (*GP*). To a stirred soln. of 0.25 mmol substrate **3** in 1 ml of dry MeCN is added 8.9 mg of [(*R*)-**1a** · (DME)] · MeCN or 10.3 mg of [(*R*)-**1b** · (MeCN)]. After dissolution of the metal complex, 0.30 mmol of the halogenating agent (NCS for products **5**, NBS for products **6**) is added, and the course of the reaction is followed by TLC. For workup, the reaction mixture is diluted with 20 ml of *t*-BuOMe and washed with 50 ml of H_2O.The org. phase is filtered through *ca.* 1 g of Al_2O_3, and the filtrate is washed with additional *t*-BuOMe. The solvents are removed in a rotatory evaporator to yield the crude product, which also contains the TADDOL ligand. Purification is performed by FC with *t*-BuOMe/hexane as indicated for the individual compounds.

Ethyl 2-Chloro-2-methyl-3-oxo-3-phenylpropanoate (**5a**). According to *GP*, but on a 0.378-mmol scale, with catalyst [(*R*)-**1b**(MeCN)]. FC (*t*-BuOMe/hexane 1:15): 77 mg (85%) of **5a**. Colorless oil. R_f (*t*-BuOMe/hexane 1:5) 0.47. $[\alpha]_D = +61.0$ ($c = 1.025$, MeOH; sample with 59.0% ee). IR (film, NaCl): 2983*w*, 2939*w*, 1756*s*, 1727*m*, 1695*s*, 1598*m*, 1448*m*, 1375*m*, 1263*s*, 1223*s*, 1115*s*, 1068*m*, 1013*w*, 962*m*, 860*w*, 691*m*, 688*w*. ^{1}H-NMR: 1.09 (*t*, $J = 7.1$, MeCH$_2$O); 2.01 (*s*, Me); 4.18 (*dq*, $J = 10.7$, 7.1, 1 H, MeCH_2O); 4.23 (*dq*, $J = 10.7$, 7.1, 1 H, MeCH_2O); 7.40–7.47 (*m*, 2 arom. H); 7.52–7.59 (*m*, 1 arom. H); 7.97–8.02 (*m*, 2 arom. H). ^{13}C-NMR: 13.6 (Me); 26.1 (Me); 63.1 (CH$_2$); 68.5 (C); 128.4 (CH); 129.5 (CH); 133.2 (C); 133.4 (CH); 169.2 (C); 189.2 (C); ESI-MS (pos. ion): 258.2 (100, $[M + \mathrm{NH_4}]^+$). Anal. calc. for $C_{12}H_{13}ClO_3$ (240.69): C 59.88, H 5.44; found: C 60.00, H 5.50.

Ethyl 2-Chloro-2-methyl-3-(naphthalen-2-yl)-3-oxopropanoate (**5b**). According to *GP*, with catalyst [(*R*)-**1b** (MeCN)]. FC (*t*-BuOMe/hexane 1:15): 63 mg (87%) of **5b**. Colorless oil. R_f (*t*-BuOMe/hexane 1:5) 0.47. $[\alpha]_D = +62.3$ ($c = 0.77$, MeOH; sample with 63.1% ee). IR (film, NaCl): 2982*w*, 1755*s*, 1726*m*, 1690*s*, 1627*m*, 1596*w*, 1465*w*, 1444*m*, 1375*m*, 1272*s*, 1241*m*, 1219*m*, 1193*m*, 1111*m*, 1067*w*, 1018*w*, 976*w*, 938*w*, 912*w*, 866*w*, 827*w*, 757*w*. ^{1}H-NMR: 1.07 (*t*, $J = 7.1$, MeCH$_2$O); 2.07 (*s*, Me); 4.21 (*q*, $J = 7.1$, MeCH_2O); 7.51–7.64 (*m*, 2 arom. H); 7.84–7.89 (*m*, 2 arom. H); 7.92–7.97 (*m*, 1 arom. H); 8.02 (*dd*, $J = 8.7$, 1.9, 1 arom. H); 8.57 (*d*, $J = 1.9$, 1 arom. H). ^{13}C-NMR: 13.7 (Me); 26.1 (Me); 63.2 (CH$_2$); 68.7 (C); 124.9 (CH); 126.9 (CH); 127.7 (CH); 128.3 (CH); 128.9 (CH); 129.8 (CH); 130.5 (C); 131.5 (CH); 132.2 (C); 135.5 (C); 169.4 (C); 189.2 (C). ESI-MS (pos. ion): 308.2 (100, $[M + \mathrm{NH_4}]^+$). Anal. calc. for $C_{16}H_{15}ClO_3$ (290.74): C 66.10, H 5.20; found: C 66.11, H 5.49.

Benzyl 2-Chloro-2-methyl-3-oxobutanoate (**5c**). According to *GP*, but with 206 mg of **3c** (1 mmol), 4 ml of MeCN, 100 mg of molecular sieves (3 Å), 35.5 mg (0.05 mmol) of catalyst [(*R*)-**1b**(MeCN)], and 154 mg of NCS (1.15 mmol) at 0°. FC (*t*-BuOMe/hexane 1:15) gave 204 mg (85%) of **5c**. Colorless oil. R_f (*t*-BuOMe/hexane 1:5) 0.47. $[\alpha]_D = -4.0$ ($c = 1.215$, MeOH; sample with 48.0% ee). IR (film, NaCl): 3066*w*, 3034*w*, 3001*w*, 2940*w*, 1750 (sh), 1732*s*, 1456*m*, 1358*m*, 1262*s*, 1122*s*, 1101*m*, 1075*m*, 753*m*, 698*m*. ^{1}H-NMR: 1.84 (*s*, Me); 2.30 (*s*, MeCO); 5.23 (*d*, $J = 17.1$, 1 H, PhCH_2); 5.26 (*d*, $J = 17.1$, 1 H, PhCH_2); 7.30–7.42 (*m*, 5 arom. H). ^{13}C-NMR: 24.1 (Me); 25.1 (Me); 68.4 (CH$_2$); 70.6 (C); 128.1 (CH); 128.6 (CH); 128.6 (CH); 134.5 (C); 167.7 (C=O); 198.5 (C=O). EI-MS: 241 (7, M^+), 205 (79, $[M - \mathrm{Cl}]^+$), 198 (53), 181 (16), 162 (65), 91 (100, $C_7H_7^+$). Anal. calc. for $C_{12}H_{13}ClO_3$ (240.69): C 59.88, H 5.44; found: C 59.82, H 5.43.

Diphenylmethyl 2-Chloro-2-methyl-3-oxo-pentanoate (**5d**). According to *GP*, with catalyst [(*R*)-**1b**(MeCN)]. FC (*t*-BuOMe/hexane 1:15): 78 mg (94%) of **5d**. Colorless oil. R_f (*t*-BuOMe/hexane 1:5) 0.59. $[\alpha]_D = -5.6$ ($c = 1.17$, MeOH; sample with 88.2% ee). IR (film, NaCl): 3032*w*, 2982*w*, 2939*w*, 1753 (sh), 1732*s*, 1496*w*, 1449*w*, 1375*w*, 1257*s*, 1231*s*, 1122*s*, 1088*m*, 955*w*, 746*m*, 699*s*, 602*w*. ^{1}H-NMR: 1.01 (*t*, $J = 7.2$, MeCH$_2$); 1.86 (*s*, Me); 2.48 (*dq*, $J = 18.3$, 7.1, 1 H, MeCH_2); 2.73 (*dq*, $J = 18.3$, 7.1, 1 H, MeCH_2); 6.91 (*s*, Ph$_2$CH); 7.25–7.39 (*m*, 10 arom. H). ^{13}C-NMR: 8.1 (Me); 24.4 (Me); 31.0 (CH$_2$); 71.0 (C); 79.4 (CH); 126.9 (CH); 127.1 (CH); 128.3 (CH); 128.4 (CH); 128.6 (CH); 128.6 (CH); 138.8 (C); 138.8 (C); 167.1 (C); 201.7 (C). ESI-MS (pos. ion): 348.3 (100, $[M + \mathrm{NH_4}]^+$). Anal. calc. for $C_{19}H_{19}ClO_3$ (330.81): C 68.98, H 5.79; found: C 68.85, H 5.98.

*2,6-Di-(*tert*-butyl)-4-methyl 2-Chloro-2-methyl-3-oxopentanoate* (**5e**). According to *GP*, with catalyst [(*R*)-**1b**(MeCN)]. FC (*t*-BuOMe/hexane 1:20): 89 mg (97%) of **5e**. Colorless oil. R_f (*t*-BuOMe/hexane 1:5) 0.79. $[\alpha]_D = -1.2$ ($c = 0.985$, MeOH; sample with 11.4% ee). IR (film, NaCl): 2965*s*, 1761*s*, 1725*s*, 1597*w*, 1444*m*, 1417*m*, 1365*m*, 1269*m*, 1206*s*, 1173*s*, 1099*s*, 971*w*, 890*w*, 859*m*, 746*w*, 697*w*. ^{1}H-NMR: 1.11 (*t*, $J = 7.1$, MeCH$_2$); 1.30, 1.33 (2*s*, 2 *t-Bu*); 2.09 (*s*, Me–C(2)); 2.31 (*s*, Me–C(4′)); 3.00 (*dq*, $J = 18.9$, 7.1, 1 H, MeCH_2); 3.07 (*dq*, $J = 18.9$, 7.1, 1 H, MeCH_2); 7.13 (*q*, $J = 1.8$, 2 arom. H). ^{13}C-NMR: 8.3 (Me); 21.4 (Me); 25.7 (Me); 31.3 (Me); 31.4 (Me); 32.1 (CH$_2$); 35.3 (C); 35.4 (C); 71.2 (C); 127.2 (CH); 127.3 (CH); 135.3 (C); 141.9 (C); 142.1 (C); 146.3 (C); 167.5 (C); 203.1 (C). ESI-MS (pos. ion): 384.3 (100, $[M + \mathrm{NH_4}]^+$). Anal. calc. for $C_{21}H_{31}ClO_3$ (366.92): C 68.74, H 8.52; found: C 68.88, H 8.66.

Ethyl 2-Bromo-2-methyl-3-oxo-3-phenylpropanoate (**6a**). According to *GP*, with catalyst [(*R*)-**1a**(DME)] · MeCN. FC (*t*-BuOMe/hexane 1:15): 60 mg (84%) of **6a**. Colorless oil. R_f (*t*-BuOMe/hexane 1:5) 0.45. $[\alpha]_D = +8.8$ ($c = 0.96$, MeOH; sample with 8.5% ee). IR (film, NaCl): 3062*w*, 2983*m*, 2936*w*, 2905*w*, 1752*s*, 1722*s*, 1689*s*, 1597*m*, 1583*w*, 1447*m*, 1375*m*, 1260*s*, 1223*s*, 1187*w*, 1109*s*, 1061*m*, 1013*m*, 961*s*, 859*w*, 808*w*, 730*w*, 690*m*, 667*w*, 633*w*. ^{1}H-NMR: 1.08 (*t*, $J = 7.2$, MeCH$_2$O); 2.18 (*s*, Me); 4.16, 4.23 (*C* and *D* of A_3CD, $J_{CD} = 10.8$, $J_{AC} = J_{AD} = 7.2$, MeCH_2O); 7.39–7.48 (*m*, 2 arom. H); 7.51–7.59 (*m*, 1 arom. H); 7.96–8.02 (*m*, 2 arom. H). ^{13}C-NMR: 13.6 (Me); 27.2 (Me); 60.8 (C); 63.3 (CH$_2$); 128.4 (CH); 129.5 (CH); 133.3 (CH); 133.3 (C); 169.1 (C=O); 189.2 (C=O). ESI-MS (pos. ion): 302.1, 304.1 (100, $[M + \mathrm{NH_4}]^+$). Anal. calc. for $C_{12}H_{13}BrO_3$ (285.13): C 50.55, H 4.60; found: C 50.43, H 4.75.

Diphenylmethyl 2-Bromo-2-methyl-3-oxobutanoate (**6d**). According to *GP*, with catalyst [(*R*)-**1a**(DME)] · MeCN. FC (*t*-BuOMe/hexane 1:15): 84 mg (90%) of **6d**. Colorless oil. R_f (*t*-BuOMe/hexane 1:5) 0.67. $[\alpha]_D = -5.1$ ($c = 1.08$, MeOH; sample with 22.8% ee). IR (film, NaCl): 3088*w*, 3064*w*, 3032*w*, 2982*w*, 2938*w*, 2878*w*, 1748 (sh), 1728*s*, 1496*m*, 1456*m*, 1375*w*, 1256*s*, 1230*s*, 1186*m*, 1118*s*, 1081*m*, 955*m*, 915*w*, 745*m*, 700*s*, 646*w*, 601*w*.

^{1}H-NMR: 1.02 (*t*, *J* = 7.2, *Me*CH$_2$); 2.01 (*s*, Me); 2.52 (*dq*, *J* = 17.9, 7.2, 1 H, MeC*H*$_2$); 2.78 (*dq*, *J* = 17.9, 7.2, 1 H, MeC*H*$_2$); 6.91 (*s*, Ph$_2$C*H*); 7.26 – 7.38 (*m*, 10 arom. H). ^{13}C-NMR: 8.6 (Me); 25.4 (Me); 31.5 (CH$_2$); 62.8 (C); 79.5 (CH); 126.9 (CH); 127.1 (CH); 128.3 (CH); 128.4 (CH); 128.6 (CH); 128.6 (CH); 138.8 (C); 138.9 (C); 167.3 (C=O); 201.2 (C=O). ESI-MS (pos. ion): 392.1, 394.1 (100, [*M* + NH$_4$]$^+$). Anal. calc. for $C_{19}H_{19}BrO_3$ (375.26): C 60.81, H 5.10; found: C 60.84, H 5.27.

*(*S*)-*N*-Chloro-*N*-(1-phenylethyl)methanesulfonamide* (**8**). To a soln. of 2.00 g *(*S*)-*N*-(1-phenylethyl)methanesulfonamide* (**7**) [23] in 10 ml CH$_2$Cl$_2$ were added 40 ml of aq. NaOCl soln. (*ca.* 13%) and 50 mg of NBu$_4$HSO$_4$. After stirring for 2 h, the org. phase was washed twice with H$_2$O and dried (MgSO$_4$). On evaporation, 2.135 g (91%) of **6** was obtained as a faintly yellow oil, purity *ca.* 95% (^{1}H-NMR). Samples for chlorination experiments and analysis were purified by FC (*t*-BuOMe/hexane 1 : 5). Colorless oil. R_f (*t*-BuOMe/hexane 1 : 2). IR (film, NaCl): 3031*w*, 2936*w*, 1496*w*, 1455*m*, 1355*s*, 1164*s*, 1057*m*, 962*m*, 934*m*, 852*w*, 780*w*, 764*m*, 700*m*. ^{1}H-NMR: 1.71 (*d*, *J* = 6.8, *Me*CH); 2.76 (*s*, MeSO$_2$); 5.43 (*q*, *J* = 6.8, MeC*H*); 7.33 – 7.53 (*m*, 5 arom. H). ^{13}C-NMR: 17.8 (Me); 36.7 (Me); 61.2 (CH); 128.1 (CH); 128.5 (CH); 128.8 (CH); 137.3 (C). EI-MS: 235/233 (0.07/0.16, *M*$^+$), 197 (8, [*M* – Cl]$^+$), 184 (100), 120 (52), 106 (68), 104 (68), 77 (47), 51 (17), 42 (10). Anal. calc. for $C_9H_{12}ClNO_2S$ (233.72): C 46.25, H 5.17, N 5.99; found: C 46.38, H 5.15, N 6.19.

Catalytic Chlorination with **8**. To a soln. of 0.25 mmol of **3c** in 1 ml of MeCN were added 2.7 mg of CpTiCl$_3$ (0.013 mmol, 5 mol-%) (or alternatively 8.9 mg of [(*R*)-**1a** · (DME)] · MeCN) and 70 mg (0.30 mmol) **8**. Workup as described in *GP*. The raw products were directly subjected to HPLC analysis.

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